The basis of the present invention is the construction of a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS that is intrinsically a function of this class of molecules to permeate the mammalian BBB as an intact chemical entity. Accordingly, the chemical and pharmacological integrity of each of the receptor activating domains functionally enables BBB transport of its covalently bonded reciprocal receptor activating domain. As such, the requirement for an intact chimeric hybrid conjugate molecule as the only viable transport vehicle for equivalent BBB transport of each of its mu opioid and substance P receptor activation domains distinguishes the present invention as novel and unknown to the literature of CNS analgesic and anti-abuse drugs.

The novelty of the present invention is not predictable according to the teachings of Syvanen and coworkers (1) who studied influx and efflux processes of morphine and morphine-glucuronides in relation to their BBB permeability properties and brain concentrations. Syvanen and coworkers teach that efficacious BBB permeation is determined by a combination of influx hindrance (a gatekeeper function in the luminal membrane that is functionally linked to P-glycoprotein activation) and efflux enhancement by transporters that pick up molecules on one side of the luminal or abluminal membrane and release them on the other side. The facilitative method of BBB transport of morphine and morphine congeners by covalently bonded heterologous substance P receptor activating domains as found in the structure of chimeric hybrid conjugate molecules is not predictable by the general principle of BBB permeation by morphine and morphine congeners codified by Syvanen and coworkers. Conversely, the facilitative method of BBB transport of substance P fragments or non-peptide substance P receptor activating domains by covalently bonded heterologous morphine, morphine congeners, and opioid peptide mu opioid receptor activating domains as found in the structure of chimeric hybrid conjugate molecules is not predictable by the teachings of Syvanen and coworkers.

In light of the work of Syvanen and coworkers cited above, the teachings of Liederer and coworkers (2) provide us with guidelines by which to construct a general class of chimeric hybrid conjugate molecules that combine any non-peptide opioid with any active fragment of substance P, or any peptide, for transport across the BBB. Liederer and coworkers teach that low BBB permeation is functionally linked to strong substrate activity for P-glycoprotein and efflux transporters in this biological barrier that is markedly enhanced for a variety of tested opioid peptide analogs sharing a common covalent cyclical structure. In contrast, capped, electrically neutral, linear derivatives of a variety of opioid peptide analogs with acetylation of the N-terminal and amidation of the C-terminal ends display efficacious permeation of the BBB via low substrate activity for P-glycoprotein and efflux transporters in this biological barrier.

Application of guidelines derived from the teachings of Liederer and coworkers in reference to the teachings of Syvanen and coworkers will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1-4, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous

activation of mu opioid and substance P receptors within the CNS. Chimeric hybrid conjugate molecules that combine any non-peptide opioid with any active fragment of substance P, or any peptide, for transport across the BBB are constructed as capped, electrically neutral, linear sequences with the non-peptide opioid covalently bonded to the N-terminal end of the substance P fragment through a 4-6 carbon molecular linker and containing a neutral amide group at the C-terminal end of the substance P fragment. Chimeric hybrid conjugate molecules that combine any opioid peptide, or for that matter any peptide, with any non-peptide substance P receptor activating domain for transport across the BBB are constructed as capped, electrically neutral, linear sequences with acetylation of the N-terminal of the opioid peptide that is covalently bonded at the C-terminal end to the non-peptide substance P receptor activating domain through a 4-6 carbon molecular linker. Finally, the teachings of Schiller (3) in reference to those of Syvanen and coworkers (1) and Liederer and coworkers (2) demonstrate a permissive chemical heterocyclic substitution in the internal domains of capped linear opioid peptide sequences that allow for efficacious BBB permeation, thereby providing validation for our specification indicating d-glucuronic acid, as a representative example of a closed-ring carbon structure, as an appropriate 6 carbon linker connecting linear mu opioid and substance P receptor activating domains within chimeric hybrid conjugate molecules.

The facilitative method of BBB transport of morphine and morphine congeners by covalently bonded heterologous substance P receptor activating domains or conversely, of BBB transport of substance P fragments or non-peptide substance P receptor activating domains by covalently bonded heterologous morphine, morphine congeners, and opioid peptide mu opioid receptor activating domains, requires maintenance of opioid and substance P activities in chemically-modified structures of chimeric hybrid conjugate molecules. The teachings of Portoghese and coworkers (4, 5) in reference to those of Liederer and coworkers and Schiller provide specific indications for maintaining opioid activity following chemical modification of the multi-ringed non-peptide structures characteristic of morphinans, benzomorphans, and phenylpiperidines, as described for opioid peptide analogs. The construction of hybrid chimeric conjugates containing non-peptide opioids or chemically modified opioid peptide sequences are consistent with guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller and will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1-4, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS.

In brief, the teachings of Portoghese and coworkers provide the following guidelines for preserving high affinity mu opioid receptor activity for all non-peptide opioid domains found in the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS. Their teachings indicate that the A ring OH group at position 3 must be conserved during synthesis and/or conjugation to active substance P fragments though a linker molecule. Consistent with the major body of published opioid research, conservation of the A ring OH group at position 3 is required for high affinity mu opioid receptor

activation. Thus, the A ring OH group at position 3 may be protected during synthesis or conjugation via covalent linkage to well recognized blocking groups that include Acetyl or T-butyl moieties. Following synthesis or construction of chimeric hybrid conjugates the Acetyl or T-butyl moieties are removed by gentle chemical treatment yielding non-peptide chemical moieties with a free A ring OH group at position 3.

The teachings of Portoghese and coworkers also indicate that the B ring OH group at position 6 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure is an appropriate site for chemical modification due to its location at a point distal to the obligate A ring OH group at position 3 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure. Chemical modification and linkage of the non-peptide opioid domain of molecules of the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS at a position spatially separated and distal to the obligate A ring OH group will permit binding in a sterically unhindered fashion to the mu opioid receptor. The B ring OH group at position 6 of morphine or an equivalent position on the morphinan or benzomorphan multi-ringed structure may be further oxidized to a keto group with full retention of opioid activity. OH and keto groups are generally employed as chemical moieties capable of covalently linking discrete chemical entities through ester or ether chemistry. Finally, the teachings of Portoghese and coworkers indicate that multiple positions of the B ring, including the OH group at position 6 of morphine, or an equivalent position on the morphinan or benzomorphan multi-ringed structure, may be chemically modified without effecting opioid activity mediated by the obligate A ring OH group.

The construction of hybrid chimeric conjugates containing non-peptide opioids or chemically modified opioid peptide sequences are consistent with guidelines provided by Portoghese and coworkers, established authorities in the synthesis and structure-function relationships of non-peptide opioids, in reference to the teachings of Liederer and coworkers and Schiller and will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1-4, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS.

The teachings of Cascieri and Liang (6) and Mantyh and coworkers (7) provide specific indications for maintaining substance P activity within the class of C-terminal fragments of substance P. The rules provided by Cascieri and Liang and Mantyh and coworkers are considered to be general rules for evaluating bioactivities of fragments of substance P by established investigators in substance P research. According to their teachings and consistent with generally accepted formulations, all fragments of substance P maintaining a fully intact C-terminal peptide domain equal to or greater than 5 amino acids have been determined to possess biological activity using a variety of testing paradigms. In the present invention, biologically active fragments of substance P include substance P 3-11, substance P 4-11, substance P 5-11, substance P 6-11, and substance P 7-11. All biologically active substance P fragments contain only one free alpha amino group that is located at a site distal to substance P receptor recognition domain and is

utilized as the point of linkage of all active fragments of substance P within the structure of the class of chimeric hybrid molecules described in the present invention. In sum, the teachings of Cascieri and Liang and Mantyh and coworkers in reference to the teachings of Portoghese and coworkers, Liederer and coworkers, and Schiller provide guidelines that will enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with Claims 1-4, i.e., a general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS.

A. Chimeric hybrid conjugate molecules that combine *any non-peptide opioid with any active fragment of substance P, or any peptide, for transport across the BBB* are constructed as capped, electrically neutral, linear sequences with the non-peptide opioid covalently bonded to the N-terminal end of the substance P fragment through a 4-6 carbon molecular linker, or according to the teachings of Schiller (3) a more complex heterocyclic structure, and containing a neutral amide group at the C-terminal end of the substance P fragment. Figure 1 depicts the construct of a linear chemical structure within the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS that contains a representative member of the morphinan, benzomorphan, or phenylpipcridine classes of non-peptide opioid alkaloid in covalent linkage to a representative member of the class of 4-6 carbon or more complex heterocyclic molecular linker in covalent linkage to a representative member of the class of biologically active fragments of substance P that include substance P 3-11, substance P 4-11, substance P 5-11, substance P 6-11, and substance P 7-11, and their chemically modified congeners.

Figure 1: Construct of a chimeric hybrid conjugate molecule that combines any non-peptide opioid with any active fragment of substance P

Non-peptide opioid alkaloid	Molecular linker	Active fragment of substance P

Representative candidate molecules chosen from the morphinan, benzomorphan, or phenylpiperidine classes of non-peptide opioid alkaloids, 4-6 carbon or more complex heterocyclic molecular linkers, and biologically active fragments of substance P are listed in Table 1 and one of each may be covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules according to guidelines gleaned from the teachings of Portoghese and coworkers (4, 5), Cascieri and Liang (6) and Mantyh and coworkers (7) in reference to those of Liederer and coworkers (2) and Schiller (3).

Table 1: Representative molecules covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules that combine any non-peptide opioid with any active fragment of substance P for transport across the BBB.

Non-peptide opioid alkaloids	Molecular linkers	Active fragments of substance P
Morphine	Succinic acid	substance P 3-11

Dihydromorphine	Gamma hydroxybutyric	substance P 4-11
Oxymorphone	acid	substance P 5-11
Oxycodone	d-glucuronic acid	substance P 6-11
Hydrocodone	l-glucuronic acid	substance P 7-11
Pentazocine	oxaloacetic acid	D-nor-leu substance P 3-11
Cyclazocine	alpha ketoglutaric acid	D-nor-leu substance P 4-11
Fentanyl	inositol	D-nor-leu, D-tryp substance
Sufentanyl	tetrahydroisoquinoline-3-	P 3-11
	carboxylic acid	D-nor-leu, D-tryp substance
		P 4-11

B. Chimeric hybrid conjugate molecules that combine *any mu opioid receptor-preferring opioid peptide, or for that matter any peptide, with any non-peptide substance P receptor activating domain* for transport across the BBB are constructed as capped, electrically neutral, linear sequences with acetylation of the N-terminal of the opioid peptide that is covalently bonded at the C-terminal end to the non-peptide substance P receptor activating domain through a 4-6 carbon molecular linker, or according to the teachings of Schiller (3) a more complex heterocyclic structure. Figure 2 depicts the construct of a linear chemical structure within the general class of chimeric hybrid conjugate molecules capable of simultaneous activation of mu opioid and substance P receptors within the CNS that contains a representative member of the class of mu opioid receptor-preferring opioid peptide in covalent linkage to a representative member of the class of 4-6 carbon or more complex heterocyclic molecular linker in covalent linkage to a representative member of the class of non-peptide substance P receptor activating domain.

Figure 2: Construct of a chimeric hybrid conjugate molecule that combines any mu opioid receptor-preferring opioid peptide with any non-peptide substance P receptor activating domain.

Mu opioid receptor-preferring opioid peptide	Molecular linker	Non-peptide substance P receptor activating domain

Representative candidate molecules chosen from the class of mu opioid receptor-preferring opioid peptides, 4-6 carbon or more complex heterocyclic molecular linkers, and non-peptide substance P receptor activating molecules are listed in Table 2 and one of each may be covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules according to guidelines gleaned from the teachings of Portoghese and coworkers (4, 5), Cascieri and Liang (6) and Mantyh and coworkers (7) in reference to those of Liederer and coworkers (2) and Schiller (3).

Table 2: Representative molecules covalently incorporated into the linear sequences of chimeric hybrid conjugate molecules that combine any mu opioid receptor-preferring opioid peptide with any non-peptide substance P receptor activating domain for transport across the BBB.

Mu opioid receptor-preferring opioid peptides	Molecular linkers	Non-peptide substance P receptor activating molecules
N-acetyl methionine enkephalin N-acetyl methionine enkephalin-Arg-Phe N-acetyl, D-ala2, methionine enkephalin N-acetyl leucine enkephalin N-acetyl leucine enkephalin-Arg-Gly-Leu N-acetyl,D-ala2, leucine enkephalin N-acetyl dynorphin A (1-13) N-acetyl endomorphin 2	Succinic acid Gamma hydroxybutyric acid d-glucuronic acid l-glucuronic acid oxaloacetic acid alpha ketoglutaric acid inositol tetrahydroisoquinoline-3-carboxylic acid	L-733,061 (partial agonist) GR7362 RP67580 (partial agonist)

The Specification is amended as per the attached amended Specification.

The Sequence Listing is amended as per the attached amended Sequence Listing.

Response to Paragraph 6

I respectfully submit that my response to paragraphs 4 and 5 provides sufficient rationale to overturn double patenting rejections provided by 6,881,829 and 6,759, 520.

Response to Paragraph 7

I respectfully submit that my response to paragraphs 4 and 5 provides sufficient rationale to overturn prior art rejections provided by 6,759, 520.

Response to Paragraph 8

Claims 1-4 are novel and unpredictable by the teachings of Wainer and coworkers. Wainer and coworkers teach that morphine is covalently linked to BSA via a succinyl bond at position 3. The procedure of Wainer and coworkers is a method for generating antibodies to morphine via conjugation to a large protein BSA that by its chemical nature does not cross the BBB. Antibody production is generally believed to be functionally linked to processing of antigen or hapten linked to carrier protein in the blood. By definition, antisera contain antibody molecules generated by white blood cell processes in the peripheral circulation. Accordingly, Wainer and coworkers teach that conjugation of morphine to BSA effectively represents a peripheral blood pool of conjugated morphine that is never meant to cross the BBB. Furthermore, as discussed in

our rebuttal to points 4 and 5 above, the teachings of Wainer and coworkers link morphine to BSA through the A ring OH group at position 3, thereby inactivating the opioid receptor binding activity of morphine. The teachings of Wainer and coworkers are therefore not functionally linked to prior observations of Foran and coworkers and do not provide unpatentable criteria by which to reject Claims 1-4.

Materials Cited Above

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Respectfully yours,

Attachments
Amendment No. 2 to Claims
Amended Specification
Amended Drawings
Amended Sequence Listing

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I certify that this correspondence is being filed by fax to ~~703-872-9306~~ on the date below.

Date: May 15, 2006

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